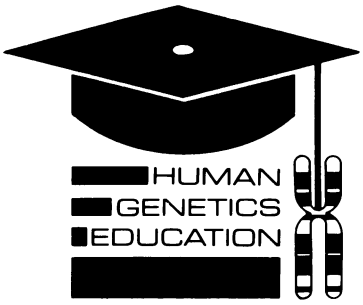
Am. J. Hum. Genet. 49:475–487, 1991



FEATURE ARTICLE
Defining the Gene: An Evolving Concept

Elof Axel Carlson

Department of Biochemistry and Cell Biology, State University of New York at Stony Brook

Some terms such as "life," "love," and "reality" defy adequate definition when relentlessly pursued through all their subtleties and complex exceptions. They are essential terms nevertheless and normal conversation would be impossible if each term were to bear its load of nuances and logical traps. So too the term "gene" presents a difficulty for simple definition when each generation of scientists finds new difficulties with older definitions that sufficed. For normal discourse the gene is the unit of heredity associated with a specific transmissible trait. In that vague sense it permits students to follow Mendel's laws; it enables geneticists to design genetic schemes for inserting or combining a variety of genetic traits in plasmids, fruit flies, maize, or humans; and it gives counselors the satisfaction that clients can grasp what will happen to their offspring if they reproduce with their spouses.

For the scientist trying to understand how genes work, what they are associated with, and how they are organized both chemically and structurally, this simple level of the gene as the unit of heredity breaks down. It broke down as early as 1910 when the new term "gene" was competing with its sibling synonyms "unit character," "unit factor," "factor," "character unit," or Mendel's (1966) own "elemente." The term "gene" arose from Darwin's (1868) provisional theory of pangenesis, an erroneous theory of heredity, somewhat Lamarckian, that proposed minute units, gemmules, that floated from cell to cell and ended up as composites in the germinal tissue. De Vries took over the theory some 20 years later and developed a concept of "intracellular pangenesis." The units (now renamed "pangenes") had the property of mutation, and various combinations in number and kind would determine varietal differences. By 1902 De Vries was advocating the origin of species and varieties by mutation (not in the modern sense but by sudden appearances, known as "saltations"). Darwin had rejected sudden mutations (then called "sports") as a basis for speciation. De Vries thought he had found evidence for such new species in the evening primrose (*Oenothera*).

Johannsen liked De Vries's theory and chopped the prefix off the units and in 1909 called them genes. He had the wisdom to leave the gene undefined and to request that his simple term replace all those other terms that implied some specific structure or function. The term caught on but challenged every geneticist to try out some definition based on research that seemed to give this term specificity. The term "genetics" was coined in 1906 by Bateson and thus has an independent origin. Both "gene" and "genetics" share a Greek root (*gen*, for origins), as seen in the more familiar term "genesis." In the next 30 years genes were seen as compound structures, like bean bags, filled with smaller "genomeres" (Eyster 1924), and they were extended from maize to *Drosophila* by Demerec (1926) with his "mutable genes." The genomere model assumed, erroneously, that a large number of identical units acted as a gene. The model was invented to explain both spotting in the kernels of corn and variegated traits ("mutable genes") in some species of fruit flies. The genomere model did not last long, and a major test of it was carried out by Muller (1928) when he first induced mutations with x-rays. He found some mosaic mutations in the F1 generation (and not in later generations), but he interpreted this as a "doubleness" of the chromatid or genetic thread in the sperm that was x-rayed. The discovery of the molecular basis of the doubleness came some 25 years later with the working out of the double helical structure of DNA.

Genes were seen as linked units along the length of the chromosome and as having a determinable length and number in the genome of the organism studied (by

Received June 17, 1990; final revision received April 9, 1991.

Address for correspondence: E. A. Carlson, Distinguished Teaching Professor, Department of Biochemistry and Cell Biology, State University of New York at Stony Brook, Stony Brook, NY 11794–5215.

© 1991 by The American Society of Human Genetics. All rights reserved.
0002-9297/91/4902-0037$02.00

Morgan and his students from 1910 to 1915). They were equated with bands, or with part bands (as in the analysis of the yellow-achaete-scute region by Muller and Prokofyeva [1935]), in the giant salivary chromosomes of fruit flies (Painter 1934; Bridges 1936; Muller 1936*a*). They were measured by target theory as physicists and geneticists equated them with atoms subject to bombardment by x-rays. In this approach, one assumed that the gene was a floating target in a specific spatial volume. The size of the target in the space would determine how frequently it was hit by a given amount of radiation. The assumptions for target theory were vague and this model did not succeed for the gene (but it succeeded for Preer [1948] when he showed that Sonneborn's [1949] plasmagene kappa factors were likely to be visible by optical microscopy and when they turned out to be the size of small bacteria). Genes were likened to autocatalysts (self-replicating enzymes), to viruses (as Muller pointed out in 1922, there was no empirical way to distinguish a virus from a "naked gene" [Muller 1922]), and to crystals with a unique copying mechanism (a view favored by Muller in 1936 [1936*b*]), as well as to "aperiodic crystals" with a "codescript" (views of the gene popularized by Schrödinger [1945] in his best selling book *What is Life?*).

The later fate of the gene concept included a compound analysis into "gene nests," "complementation units," and "pseudoalleles." These three concepts of complex organization of genes were at the forefront of genetic thinking from the 1930s to the 1950s. Systems such as the dumpy alleles were considered by Muller to be what he called "gene nests" because the number of alleles was large, because they expressed effects in different organs or at different stages of development, and because they could not be rendered conceptually into simple structural models (e.g., linear or circular; see Carlson 1959). Complementation was first worked out by Agol and Serebrovsky in the early 1930s (they used the term "step-alleles") by using the yellow-achaete-scute region of fruit flies. They thought that different combinations of bristles were under the control of different smaller genes (step-alleles) whose existence they inferred by looking for bristles removed in common by flies heterozygous for two different alleles (a status called "heteroallelic" today). The concept of complementation was revived during the 1950s when similar techniques were used to describe elaborate complementation maps which may have had little to do (in some multiple allelic series) with the sequence of genes being studied or the structure of the products they make. The term pseudoallele was introduced by McClintock (1944) and later used by Oliver (1940), Green and Green (1956), and especially Lewis (1945) to interpret what they believed were duplicate genes undergoing evolutionary divergence.

Today these older ideas about human genes have been assimilated into the discoveries of duplicate genes (tandem identical sequences for each gene), non-allelic but neighboring genes with many mutually identical conserved sequences (such as the beta and delta hemoglobin genes) and pseudogenes (sequences lacking essential sequences for transcription) found in clusters for common functions, such as the alpha gene family or the beta gene family for the hemoglobins. The sequencing of nucleotides has established numerous instances of intragenic crossing over (often unequal) leading to altered alleles and inserted or deleted bits of a gene in related genes found in these gene families. There are even occasional idiosyncratic genes within other genes and, in some viruses, one sequence of DNA serving to encode the information for two different proteins (by a slight shift of the initial nucleotide for transcriptional reading). While these rarities are intriguing and will provide much insight into the past history of gene functions, they do not negate the almost universal relation of the informational gene (i.e., the one inferred from either its mRNA or the protein product it produces) to a single protein product that corresponds to it according to the genetic code that is virtually universal. No doubt the working out of the human genome project will occupy many geneticists with the historical (evolutionary) reconstruction of genes, their alleles, and their cognate nonallelic genes both ancestral and descendant. It is a task similar to earlier attempts, by the Texas school of Patterson (1943) and Stone (1949), to reconstruct the chromosomal evolution by banding analysis of salivary chromosomes among the Drosophilidae.

The identification of nucleic acid as the chemical basis for heredity soon led to the double helical model of DNA structure (Watson and Crick, 1953*b*) and the modern era of gene studies. Recombination studies in viruses (Benzer 1955) and bacteria (Demerec et al. 1955) in 1955 provided a set of operational definitions that at first replaced and then faded away from the elusive yet ever serviceable term "gene." Genes became "cistrons" and "recons" and "mutons" (Benzer 1955). As their names implied, the units of function, recombination, and mutation used to define or detect the existence of a gene did not share a common size. Only the naive believed they did because geneticists (such as

Offermann [1935] and others in Muller's school) had long debated the relation of gene size and structure to multiple allelism, position effect, and complementation (step-allelism). The terms "recon" and "muton" failed to catch on because the molecular basis of mutation and recombination quickly made them obsolete. The cistron's original appeal was its simple functional test. It was the unit that functionally complemented a contiguous unit. It was also a concept that made molecular sense. The number of sites within it roughly corresponded to the number of nucleotides inferred from its product. It has fallen out of favor because eukaryotic genes have a more complex organization of informational and intervening sequences that cannot accommodate the simple assumptions of function and structure that are tied to the term "cistron."

These early molecular insights into the gene were premised on a widely believed theory that the gene (DNA), its message (RNA), and its product (protein) were colinear (and evidence for that was provided by Yanofsky et al. [1964]). Two discoveries shattered that oversimplified view. Genes turned out to have associated regulators, and, in eukaryotic cells, the genes had a complex organization of informational and intervening sequences of DNA. The regulation of genes was first successfully explained by the operon theory (Jacob and Monod 1961), the static gene becoming a dynamic gene not in the vague physiological way that Goldschmidt (1938) had thought it to be many years earlier but in a defined way, with regulatory genes, operators, promoters, and other up- and downstream components that determined when a gene was on or off and how rapidly its products spewed forth.

The operon model preserved the reductionist mechanical model of feedback systems involving gene products and special genetic regions that responded to them like switches. In contrast, Goldschmidt's many attempts to develop a dynamic gene model in the 1920s and 1930s led to few experiments, because they were vague and did not make good predictions. He believed that a gene was like the note of a violin string and that the entire chromosome was the gene, that our designation of the gene was merely an indication of where a node for vibration should be. He also favored a massive reorganization of the genome or chromosomes to account for more complex polymorphic mutations that usually failed to transmit or survive and that represented a "hopeful monster" for speciation (Goldschmidt 1938). These were not ideas that found favor with the more reductionist approaches of Morgan and his students.

As the molecular tools for purifying, isolating, and sequencing genes became more numerous the gene shifted from a contiguous unit of informational nucleotides to a compound gene (utterly different from Eyster's and Demerec's model). Eukaryotic genes were discontinuously organized into exons (informational units) with intervening introns (noninformational regions), and elaborate splicing methods were sought for and found to convert the dispersed informational chunks of DNA into the essential contiguous genetic message, at the level of mRNA, for proper protein synthesis. The compound nature of genes composed of exons and introns defies an easy definition of the gene such as Benzer attempted with his operational terms. Some genes may contain dozens of exons. The great advantage of such smaller informational units is their utility for assemblage into more complex proteins, composed of regional domains that are associated with specific exons. For the study of evolution of complex proteins, the shifting about of exons and the conservation of most of their sequences permits comparative studies of gene and protein evolution. A similar harvest of evolutionary information resides in the comparison of DNA sequences of nuclear and plasmid DNAs. The codons agree in all except a few instances, differing for stop signals and one or two amino acids.

Complicating the association of genes with DNA is the large amount of DNA that is neither intronic nor extronic but highly repetitive. Some repetitive DNA is informational (that which produces tRNA or rRNA), but the functions of most repetitive DNA, whether of short length (about 200 bp) or long length (about 5,000 bp) is not known. Fortunately the definition of a gene is not dependent on a universal code, a universal organization, or a specific metabolic function. About the only constant feature that distinguishes a gene from nongenic molecules is the gene's ability to copy its mutations (convariant replication) and still serve as a unit of hereditary transmission, a concept first recognized and promoted by Muller in 1922 (Muller 1922).

Biochemists will favor definitions of a gene at the molecular level, and population geneticists will favor a definition of a gene as a unit of transmission. Between these two levels of conceptual understanding there are numerous complications reflecting the diversity of living systems, from viroids to eukaryotes. The gene may be considered at the level of what is transcribed from

the DNA or what is translated from the ultimate part of the mRNA that encodes the amino acids in the protein produced by the gene. There will be those who include the introns in the gene, others who will include the reading initiation and accessory DNA promoters and regulatory receptors contiguous to the gene (but not those DNA elements removed from the gene as upstream or downstream enhancers or regulators). When even more complex genes—such as those involved in the immune-system antibody formation—are added to this search for an all-encompassing definition of the gene, the pursuit becomes quixotic. It is important that geneticists recognize the many levels at which genes can be perceived, but it is not helpful to select one of these levels and arbitrarily designate that as the universal definition of a gene. For most undergraduate students, medical students, and those who are not engaged in research in genetics, the gene in its functional sense is more helpful than the gene in its complex biochemical or molecular sense. One does not need to be an expert in genetic transcription and translation to convey to a family the risks they face when a grandparent is diagnosed as having Huntington disease.

Those trained as geneticists after Morgan and his students successfully challenged contending theories of heredity and the nature of the gene do not realize how much of a legacy we owe to Bateson's ideas and efforts in wresting genetics from a much more limited and vague collection of nineteenth-century beliefs. At the turn of the century it was widely believed in England that heredity involved numerous subtle variations of a fluctuating kind. The study of heredity was believed possible only through mathematical analysis, and Galton and Pearson led a biometric movement to provide a quantitative basis for evolutionary studies. Galton was also sympathetic to discontinuities in evolution or heredity but had no effective model (other than an instability of whatever the hereditary factors were). Bateson challenged this prevailing view and promoted discontinuous variation as worthy of study. When Mendelism was rediscovered, he became its champion and extended it to animals and helped shape the vocabulary and thinking for working with Mendelism. It was accomplished through his persistent belligerence, taking on a majority opinion that did not hesitate to reject his papers and force him to publish his views privately at his own expense (his 1902 book, *Mendel's Principles of Genetics—A Defence*, took on the establishment).

The last historical survey of the gene concept (Carlson's *The Gene: A Critical History [1966]*) ended its study in 1960. In the 30 years that have since passed, the major conceptual challenges to defining it have come from the eukaryotic organization of genes and the accessory sequences that are associated with the transcription of a gene. They make any attempt at simple colinearity of information difficult, but they do not destroy the essential truth of the central dogma. Information for making proteins in cells does flow from DNA to mRNA to protein. The set of exons (arising from a properly processed RNA resulting in an mRNA or even in a complementary DNA produced from the mRNA) does correspond to the predicted number of amino acids in its protein. The fact that certain viruses do shift from RNA to DNA by using a reverse transcriptase (Baltimore 1970; Temin and Mizutani 1970) does not negate the informational flow which goes to protein. There is no evidence for a protein to DNA reversal of information, although this is a conceivable possibility and one that Lamarckian geneticists have hoped to find to vindicate an environmentally directed evolution in which the environment does not have to be limited to the role of a sifter for natural selection. While there may some day be a protein to RNA flow of information, it is unlikely to play a major role in cellular systems whose proteins are not randomly tossed together, or even altered, without some preexisting and corresponding mutant source at the level of their nucleic acids.

The central dogma and the "informational gene" (a better term than "cistron," because it does not require the physical integrity of sequence that eukaryotic DNA lacks) have survived these apparently contradictory findings. It is harder to define the gene with operators, promoters, and upstream and downstream regulators of their transcription and frequency of transcription. They might more properly be called "accessory sequences" for gene processing because they are universal features of all (or many) genes and are not unique features of each gene. Similarly, the introns pose no problem for the definition of the gene, because they are not part of its informational gene. They can, of course, be decisive in providing mutations that affect the way the exons are assembled. If they contain bits of intronic sequences as a result of mutation, they will fail to function when their protein is eventually translated. But one could argue that this would be true for frameshift mutations occurring in clearly contiguous and unrelated genes. They can lead to chimeric

mRNA that fuses the information from two genes. The gene need not be defined by the pathology of its mutations.

More troublesome are the ways some genes are modified for their role in dosage compensation (Lyon's X inactivation), probably by methylation of the nucleotides. A similar chemical modification or "imprinting" may distinguish paternal and maternal pairs of chromosomes, with consequent malformations of seemingly diploid cells bearing a pair of autosomes that are both paternal or both maternal. Even if their exonic sequences are identical, one cannot talk about the "same" gene for two different X chromosomes, unless these chemical modifications are "epiphenomena" imposed on noninformational sequences (intronic or accessory to the exons). In that case we retain the integrity of the idea of an "informational gene," despite the physiological changes occurring elsewhere.

McClintock's (1956) discovery of transposable elements has moved from eukaryote to prokaryote to eukaryote again, with the discovery of numerous destabilizing genetic infections among some strains of fruit flies. The role of these transposable elements is by no mean settled. In some crosses they lead to mutations and chromosome breakage on a massive scale, as if they were subjected to several thousand roentgens of x-rays. There is no evidence that they play significant developmental roles in fruit fly organogenesis. They are considered by some as "genetic lice." Yet they have played a major role in generating the mutations that geneticists work with, including Morgan's own white mutation. Their capacity to shift contiguous genes around from one chromosome to another (in maize) and perhaps by lateral transfer from one species to another, may prove significant for the way genes evolve. The classical model of duplication, chromosome rearrangement, and differential mutation may not be sufficient at least in organisms with periodic visitations of transposon infections. Why some species (such as *Drosophila simulans*) are relatively free of transposable elements while their sibling species (e.g., *D. melanogaster*) are plagued with them is not known. The difference suggests that transposable elements do not force a reinterpretation of the gene. Should assigned normal developmental roles for transposons emerge, this will force geneticists to rethink what they mean when they talk about such genes.

It is difficult to assess the historical worth of recent contributions to the gene concept. Some major findings and applications of the 1980s, such as the PCR of Mullis (see Saiki et al. 1985; Mullis and Faloona 1987), seem likely to endure. Other findings will fade as newer ideas, discoveries, and applications prove more significant 10 or more years from now. I have cut this survey off at 1983 to permit that distance needed for perspective. I chose to end the survey with that year because it ushered in new techniques to isolate genes for study (chromosome walking); it initiated the molecular genetic analysis of two basic and complex processes—tumor formation (in retinoblastoma) and antibody diversity; and it provided a molecular diagnosis of gene mutations whose gene products are not known.

The 1980s also saw the emergence of the first "big science" project in genetics, the human genome project, whose chief advocate and director (for the U.S. NIH involvement) is J. D. Watson. All 23 of the human chromosomes will be mapped to within one map unit (1 cM) by this century's end, and substantial numbers of our genes will be fully sequenced. Those, like myself, who are Baconian in their scientific habits look forward to surprises as the sequencing gets underway. Those who project what is known and what seems possible from an extension of contemporary research activities may be less optimistic about the value that this approach has for adding much to our knowledge of basic genetics. All, however, agree that the mapping and sequencing of several hundred genes associated with the more familiar disorders will benefit those who seek to diagnose, treat, or prevent them.

The sequencing of genes reveals a rich harvest of pseudogenes that do not function in gene nests such as the alpha or beta hemoglobin clusters. The gene's loss of an accessory part that permits it to be transcribed renders the gene totally mutant (amorphic). It is a pathology of the gene but in a different part of its sequence. Many baroque variations of a "gene within a gene" or of chimeric functional genes that arose from the fusion of exon pieces of unrelated genes are likely to be found as the human genome project gets underway. These reflect the opportunistic ways that evolution works. If evolution implies survival, and if survival implies the functioning of an organism's gene products, then the informational sequences that produce these products are the genes—and not the curious historical provenance of their origins.

Appendix

As often happens in the history of ideas, the achievements of early contributors are marred with errors (often seen through hindsight) that may damage that

person's historical reputation. Other contributors are more fortunate, and their errors are forgotten as their contributions remain celebrated. To some degree historians of science can correct for both imbalances and enrich our understanding of how a concept or field emerged and established itself as part of our current scientific worldview. Too often, major contributors fade from memory or become demoted in our standing, for their failings. Scientists are well aware in their own careers that error, false hypothesis, and being scooped are part of doing science even if these imperfections never enter their curricula vitae or self-appraisal.

With those qualifications, it might be helpful to list the key contributors to the gene concept and identify what aspect remains part of our working concept of the gene today. For those interested in the history of human genetics, portions of Kevles's *In the Name of Eugenics* (1985) and Dronamraju's *The Foundations of Human Genetics* (1989) will be helpful. Both the relation of basic genetic findings to human genetics and the contributions of human genetics to the understanding of the gene are provided in this listing. The dates given are those of publications associated with key ideas or findings cited in the References list. They are not necessarily the date of discovery or first experimentation or observation leading to a key idea, but they are not more than a few years after that event.

Antiquity—The Bible, the Talmud, and other sources earlier than Mendel reveal an awareness of heredity and specific disorders such as hemophilia. The noncircumcision of the third son (after two hemorrhagic deaths of his brothers) suggests no sophisticated awareness in the Talmud of the X-linked basis of this disorder. Similarly, many recognitions of family transmissions for colorblindness, retinoblastoma, polydactyly, ichthyosis, and other disorders were recorded long before Mendel's paper appeared, but none proposed a specific mechanism of transmission, and none conveyed the notion of transmission by hereditary units.

1864–68: Spencer (1864); Mendel (1866); Darwin (1868)—Heredity is particulate. Spencer called them "physiological units"; Darwin called them "gemmules"; Mendel called them "elements" (*elemente*). All assumed that hereditary traits had underlying units.

1866: Mendel—The transmissible unit may be recessive, dominant, or blending. Unlike Darwin and Spencer, Mendel used his factors and assigned generic characteristics to them.

1886: Galton—Traits tend to regress to a mean. Galton inferred a polygenic basis for human variable traits such as height, weight, and shape. The inferred units, later termed "genes," were treated statistically.

1889: De Vries—The hereditary units remain in the cell. De Vries called his units "pangenes." He later (De Vries 1903) assumed that they were aligned in chromosomes, but he did not conceive that they could recombine in segments. Alterations of kind and number of pangenes—especially those alterations that led to sudden new species—constituted what he called "mutations." His "mutation theory" of speciation by saltation (1901–3) was proved wrong.

1900: Landsteiner—The ABO blood groups are discovered. Von Dungern and Hirszfeld (1910) demonstrated the genetic basis for ABO blood incompatibility which resided in the inherited antigens.

1902: Sutton—Mendel's laws are associated with meiosis. Although several cytologists surmised a relation of chromosomes to heredity, Sutton provided a model that made classical genetics possible.

1902–8: Bateson et al.—Bateson provides the vocabulary of genetics, including "heterozygote," "homozygote," and "allele" (originally "allelomorph"). He extended Mendelism to animals. Some traits are dependent on the activities of two or more hereditary units. From these epistatic relations Bateson worked out departures from Mendelian 9:3:3:1 ratios.

1908: Garrod—The first human metabolic monogenic trait is described. Alkaptonuria was described as an inherited, familial trait. Garrod called this an "inborn error of metabolism." He added albinism, pentosuria, and cystinuria as additional instances and noted the relation of recessive human traits to parental consanguity, especially cousin marriages, suggesting a recessive mode of inheritance.

1905: Farabee—The first human monogenic trait is described. Brachydactyly showed an autosomal dominant pattern of inheritance.

1906: Bateson—The term "genetics" is introduced, along with the new field it describes.

1909: Johannsen—The term "gene" is used for the hereditary unit. He lopped off De Vries's "pangenes" and left the new term, "gene," chemically and physically undefined to give it opportunity for development.

1909: Johannsen—The concept of polygenic inheritance is introduced. He distinguished phenotype from

genotype and showed that the range of variation is fixed within inbred selected pure lines of beans. Human height was quickly seen as a trait analogous to that seen in Johannsen's work on beans.

1909–10: Nilsson-Ehle (1909); East (1910)—The concept of quantitative inheritance is introduced. Two or more genes may add equally to the intensity of a trait. Quantative inheritance in cereal coat color involves two or more pairs of genes producing blond-to-red colors, with many shades of pink.

1910: Morgan—X-linked inheritance is worked out. He assigned genes to the X chromosome of fruit flies. Wilson then predicted that human red-green color deficiency and hemophilia were carried on the human X chromosome.

1911: Morgan—Genes may be mapped to specific chromosomes. Morgan used the cytological twisting seen in Janssen's (1909) meiotic chromosomes to posit both a physical exchange leading to segmental recombination and a general prediction that genes farther apart would recombine more frequently.

1913: Davenport—The concept of quantitative inheritance is applied to human skin color. His studies of miscegenation in Jamaica established at least two genes for melanin distribution in the skin after synthesis. Stern later raised the number to five pairs of genes.

1913: Sturtevant (1913b)—Gene location may be mapped on a linear representation of the chromosome. Genetic maps quickly replaced more cumbersome and erroneous models of repulsions, attractions, and gametic ratios proposed earlier by Bateson.

1913: Sturtevant (1913a)—The idea of multiple alleles is introduced. The white-eyed series in fruit flies demonstrate that a normal gene can mutate to more than one form.

1915: Morgan et al.—The minimum number and maximum size of genes are determined by using linkage maps. They incorporate Morgan's findings in a classical text including the work of Muller, Sturtevant, and Bridges. The first estimates reveal that fruit flies have more than 1,000 genes and that the gene occupies a chromosome region too small to be seen in an optical microscope if the gene were deleted.

1918: Muller—There are chief genes and modifier genes. It is not the genes that are variable but the characters or phenotype. The modifier genes (and environmental agents) affect a chief gene's expression.

1919: Muller and Altenburg—The rate of gene mutation is determinable. The first mutation rates were measured at about 1/1,000 progeny for a newly arising X-linked lethal gene mutation.

1922: Muller—Genes have the capacity for convariant replication. They reproduce their mutations, and this is a unique characteristic of life supplied only by the hereditary material.

1925: Bernstein—The human ABO series is proposed to be a multiple allelic system.

1925: Sturtevant—Genes may reversibly change function when separated from or returned to their neighboring genes (i.e., genes show position effects). Sturtevant did not interpret position effect as a normal regulatory process. It took another 30 years for molecular biologists Jacob and Monod to work out a normal process of regulation for the turning on or off of genes in metabolism and development.

1926: Muller—The gene is the basis of life. Unlike all other constituents of life, the gene specifies the characteristics of all other cellular constituents and controls the life cycle from fertilization to death, as well as through evolutionary time from the arising of the first replicating gene. Although this seems trivial or obvious today, Muller was considered a zealot for this view. Most biologists identified life as a complex dynamic interaction of components or invoked vitalist interpretations.

1926: Timofeef-Ressovsky and Timofeef-Ressovsky—The model of chief genes and modifiers applies to human monogenic traits. They called the presence or absence of the expression of a chief gene its "penetrance" and called the intensity of expression of the trait its "expressivity."

1927–28: Muller (1927); Stadler (1928)—Genes may —Genes may be mutated by ionizing radiation. Many had tried this earlier, but both Muller and Stadler used methods to measure this quantitatively and usher in the field of radiation genetics.

1929: Agol; Serebrovsky et al.—Genes may be analyzed into step-alleles (complementation units). A generation later, complementation maps were worked out in viruses, bacteria, and fungi.

1929–32: Stern (1929); Muller (1932)—Dosage compensation equalizes gene effects between the sexes. In fruit flies modifier genes equalize the dose difference between two and one X chromosomes. Three decades

later Lyon (1961) demonstrates X inactivation as the basis for human dosage compensation.

1932: Muller—Genes may be amorphic or hypomorphic (nonleaky or leaky). They mutate to a complete or partial loss of function. By using chromosome fragments bearing hypomorphic mutations, Muller showed that their effects were additive.

1934: Folling—The metabolic basis of a gene causing mental retardation is worked out. The mutant gene producing phenylketonuria is recessive.

1934: Painter—Giant salivary chromosomes in fruit flies are interpreted. Their polytene structure and immense size and numerous bands enable cytological mapping of genes on chromosomes. A generation later Caspersson develops quinacrine banding. Although the mechanism for banding in human chromosomes is non-polytenic and depends on regional differences in base pair ratios, the technique established a human parallel to salivary banding analysis.

1935–36: Bridges (1935); Muller (1936a)—Tandem duplications lead to gene evolution. Both worked this out using the Bar mutation in fruit flies. They predicted that differential mutation would eventually lead to new gene functions. Muller predicted that primary unequal crossing-over was the source of most new genes in a species (except for the first gene, all genes arise from preexisting genes).

1937: Bell and Haldane—The first human linkage map is demonstrated. Kindreds with both hemophilia and red-green color deficiency were used to work out the map distance of these two genes.

1938: McClintock—The breakage-fusion-bridge cycle in maize is worked out to explain certain spotting patterns caused by loss of damaged chromosomes. It later was interpreted (*a*) by Pontecorvo and Muller (1941) and Pontecorvo (1942) as a major cause of "dominant lethals" or aborted embryos in *Drosophila* from x-rayed sperm and (*b*) by Muller (after 1945) as the major cause of radiation sickness in heavily irradiated humans.

1940: Raffel and Muller—Gene clusters may be analyzed by radiation breakage (the "left-right test"). The same principles were later applied to deletion mapping of human genes.

1941: Beadle and Tatum—Genes are associated with specific enzymes. Their one-gene/one-enzyme theory suggested that each gene produces a specific protein. It brought genetics to biochemists's attention through biochemical pathways.

1941: Lewis—Some genes are pseudoallelic. Nests of adjacent and functionally related genes may exist, possibly through their origin as tandem repeats (Lewis 1945). Oliver (1940), who misinterpreted his finding, and Green and Green (1956) extended the findings to other multiple allelic series.

1944: Avery et al.—Genes are composed of DNA. Transformation of the pneumococcal cells suggested the entry and insertion of genes into the host cell's chromosomes.

1945: Schrödinger—The gene is an aperiodic crystal with a code-script. When *What is Life?* appeared, these ideas led physical scientists into molecular biology and stimulated their interest in the gene.

1947–48: Auerbach et al. (1947); Rapoport (1948): Genes may be mutated by chemicals. Auerbach used mustard gas, and Rapoport used ethylene oxide. They founded the field of chemical mutagenesis and provided a genetic basis for the chemotherapy of tumor cells.

1949–56: Pauling et al. (1949); Ingram (1956)—A genetic disorder's syndrome may be followed epigenetically from a single amino acid change in the protein or from a small lesion in a gene (as in hemoglobin and sickle cell anemia). Their analysis established both the existence of "molecular disease" and the entry of human genetics into molecular genetics.

1953: Watson and Crick (1953b)—DNA is a double helix. Their complementary basepaired structure ushered in the age of molecular biology, providing a testable chemical and physical model of the gene.

1953: Watson and Crick (1953a)—Mutation may involve single nucleotide replacement. Their prediction provided a test for the molecular basis of mutation. They also predicted a semiconservative replication of the genetic thread.

1954: Gamow—The genetic code uses a sequence of at least three nucleotides. His simple proof provided both the basis for the codon and the search for the genetic code. His assumption of an overlapping code proved wrong but was later observed in a few viral genes. Proof of the triplet nature of the codon was provided by Brenner's laboratory in 1961.

1955: Benzer—The operational gene is a cistron, re-

con, or muton. The concepts distinguished measurement of the gene through three different procedures.

1955: Benzer; Demerec et al. — Genes have a fine structure corresponding to their nucleotides. What Benzer called "genetic fine structure" became a map of the gene, with the smallest distance between mutant sites in a gene corresponding to a basepair.

1955: Pontecorvo — All genes are likely to show intragenic recombination. Pseudoallelism in his model was not rare, because intragenic recombination occurred in every gene he arbitrarily chose and tested.

1956: McClintock — Some genes are transposable. Her work provided the basis for interpreting transposons, plasmids, and vectors in prokaryotic and eukaryotic cells.

1958: Crick — DNA makes RNA makes protein (the genetic or central dogma). The dogma was quickly demonstrated with the isolation of mRNA and the isolation of tRNA molecules (predicted by Crick). With these components cell-free protein synthesis became possible.

1959: Freese — The molecular basis of mutation is worked out. Mutations may result from transitions or transversions after replication pairing errors.

1961: Jacob and Monod — Regulation of genes involves operators, structural genes, and regulatory genes. The regulation of genes explained adaptive enzyme formation and suggested a basis for embryonic development.

1961–66: Nirenberg and Matthaei (1961); Ochoa (1963); Khorana (1966) — All 64 possible codons are identified for function in the genetic code. The genetic code was assumed to be universal, and this permitted back-and-forth readings by geneticists of the amino acid sequences of proteins and of the nucleotide sequences of their corresponding genes.

1961: Brenner et al. — Mutations may arise from frameshifts affecting one or more genes. Frameshift mutations produce profoundly altered proteins and tend to be amorphs rather than hypomorphs.

1966–90: McKusick — Compilation of single-gene defects in humans is begun. By the ninth edition (1990) more than 4,000 determined or likely mutations are recorded.

1969: Miller and Beatty — The first visualization of the gene in action occurs. The feathery figures in Miller's electron micrographs showed the growing length of mRNA from DNA and the strands of ribosomes attached to them.

1970: Baltimore; Temin and Mizutani — Complementary DNA (via reverse transcriptase from mRNA) corresponds to the informational gene. The conversion of RNA into DNA is characteristic of certain viruses (retroviruses) some of which produce tumor cells.

1972: Jackson et al. — Restriction enzymes can be used to isolate genes or insert genes (natural or complementary DNA) where desired. Berg's recombinant DNA technology rapidly entered medicine and pharmaceutics.

1974: McKusick and Ruddle — The first detailed human gene maps are compiled from classical and molecular studies, especially RFLPs introduced by Botstein (see review [Botstein et al. 1980]).

1974–75: Arber (1974); Nathans and Smith (1975) — Restriction enzymes cut DNA at specific sequences. They were shown to provide a natural defense in some cells, by cutting viral DNA that entered.

1975: Southern — DNA pieces can be identified and isolated through gel electrophoresis and stacked nitrocellulose layers. Southern blotting permits identification and isolation of any desired chromosome fragment bearing a particular gene for which a radioactive probe is available.

1975–77: Sanger and Coulson (1975); Maxam and Gilbert (1977) — DNA (genes) can be sequenced. The sequencing of DNA established the lesions associated with human genetic disorders. It permitted both prenatal diagnosis of at-risk embryos and carrier screening of potential parents.

1977: Breathnach et al. — Eukaryotic genes are split. Ovalbumin was the first to reveal this complex structure. Chambon proposed that eukaryotic genes are organized into informational sequences (exons) and intervening sequences (introns). The number of exons may vary, some genes having more than a dozen. Eukaryotic transcription and formation of mRNA became complex.

1978: Kan and Dozy — DNA deletion used in the hemoglobin beta gene to detect hemoglobinopathy prenatally. Their work provided a model for using mutant DNA to screen or diagnose individuals at risk for genetic disorders.

1978: Maniatis—The first genome library is established. The fragments produced by restriction enzymes can be used as a reference library for locating genes on chromosomes.

1979: Khorana—A gene is synthesized. The successful construction of a sequence of nucleotides for a known gene leads the way for "gene machines" and the synthesis of any gene, including variants with introduced mutant sites to study gene function.

1980: Botstein et al.—RFLPs are used to construct a gene map of a human chromosome. McKusick, Ruddle, and others organize human gene mapping centers and conferences.

1982: Bishop and Varmus—Cellular oncogenes are discovered. Genes that are normal regulators of the cell cycle can become deregulated and lead to tumor formation.

1983: Bender et al.—Chromosome walking is introduced. By removing an end of a cloned DNA fragment bearing a known gene and hybridizing it against a genome library, another fragment bearing that terminal sequence can be isolated, and its end in turn can be used to identify another fragment, the process continuing until one reaches a telomere or other identifiable region of the chromosome.

1983: Cavanee et al.—The loss of both normal alleles of the retinoblastoma gene causes retinoblastoma. Regulation of retinoblast mitosis depends on the protein produced by the normal retinoblastoma gene.

1983: Tonegawa—A gene rearrangement mechanism for producing immunoglobulin diversity is discovered. Long a puzzle, the recombination possible by this somatic mechanism can produce thousands of specific antibodies.

1983: Gusella et al.—DNA probes are used to identify carriers of the gene for Huntington disease. Young adults at risk for this late-onset syndrome are confronted with multiple ethical difficulties.

Any list such as this is bound to be subjective and to leave out items others would include or remove. Similarly, any list will contain disputed claimants for priority. I do not claim this to be as exhaustive or as meticulously precise as a book that traces the history of the gene concept would be. The References list gives the names of coauthors of these articles, and the cited article may not be the first or earliest reference to a discovery. Often an idea or technique may emerge through several articles or initially may appear as a footnote or in an abstract. What this list does provide is an overview of how complex the gene concept is today when it bears its molecular, evolutionary, and comparative aspects. Despite this majestic and awesome list of insights into the gene and its applications, the gene in its simplest form as the unit of transmission can be used in good conscience by any physician, counselor, or scientist desiring to do so.

References

Agol IJ (1929) Stepallelomorphism in *Drosophila melanogaster*. Zh Eksp Moditsins 5:86–101 (PST catalog no 518 transl, Israel Program for Scientific Translations)

Arber W (1974) DNA modification and restriction. Prog Nucleic Acid Res Mol Biol 14:1–37

Auerbach C, Robson JM, Carr JG (1947) The chemical production of mutations. Science 105: 243:347

Avery OT, MacLeod CM, McCarty M (1944) Studies on the chemical nature of the substance inducing transformation of pneumococcal types. J Exp Biol Med 79:137–158

Baltimore D (1970) RNA-dependent DNA polymerase in virions of RNA tumor viruses. Nature 226:1209–1211

Bateson W (1906) The progress of genetics since the rediscovery of Mendel's papers. In: Lotsy JP (ed) Progressus rei Botanicae, Association Internationale des Botanites. G Fischer, Jena, pp 368–418

Bateson W, Saunders ER, Punnett R (1902–8) Experimental studies in the physiology of heredity. Rep Evol Comm R Soc 1:1–160; 2:1–154; 3:1–53; 4:1–60

Beadle GW, Tatum EL (1941) Genetic control of development and differentiation. Am Nat 75:107–116

Bell J, Haldane JBS (1937) The linkage between the genes for colour-blindness and hemophilia in man. Proc R Soc Biol 123:119–150

Bender W, Akam M, Karch F, Beachy P, Peifer M, Spierer P, Lewis EB, et al (1983) Molecular genetics of the bithorax complex in *Drosophila melanogaster*. Science 221:23–29

Benzer S (1955) Fine structure of a genetic region in bacteriophage. Proc Natl Acad Sci USA 41:344–354

Bernstein F (1925) Zusammenfassende Betrachtungen über die erblichen Blutstrukturen des Menschen. Z Induktive Abstammungs Vererbungslehre 37:237–270

Bishop JM, Varmus HE (1982) Functions and origins of retroviral transforming genes. In: Weiss R, Teich N, Varmus H, Coffin J (eds) Molecular biology of tumor viruses, part 3: RNA tumor viruses. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp 999–1108

Botstein D, White RL, Skolnick M, Davis RW (1980) Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 32: 314–331

Breathnach R, Mandel JL, Chambon P (1977) Ovalbumin gene is split in chicken DNA. Nature 270:314–319

Brenner S, Barnett L, Crick FHC, Orgel L (1961) The theory of mutagenesis. J Mol Biol 3:121–124

Bridges CB (1935) Salivary chromosome maps. J Hered 26: 60–64

——— (1936) The Bar 'gene' a duplication. Science 83:210–211

Carlson EA (1959) Allelism, pseudoallelism, and complementation at the dumpy locus in *D. melanogaster*. Genetics 44:347–373

——— (1966) The gene: a critical history. Saunders, Philadelphia. Reprinted 1990, Iowa State University Press, Ames

Cavanee WK, Dryja TP, Phillips AR, Benedict WF, Godbout R, Gallie BL, Murphree AL, et al (1983) Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature 305:779–784

Crick FHC (1958) On protein synthesis. Symp Soc Exp Biol 12:138–167

Darwin C (1868) Provisional hypothesis of pangenesis. In: Animals and plants under domestication, vol 2. Orange Judd, New York, pp 428–483

Davenport CB (1913) Heredity of skin color in Negro-white crosses. Carnegie Institution of Washington, Washington, DC

Demerec M (1926) Mutable genes in *Drosophila virilis*. Proc Int Congr Plant Sci 1:943–946

Demerec M, Blomstrand I, Demerec ZE (1955) Evidence of complex loci in *Salmonella*. Proc Natl Acad Sci USA 41: 359–364

De Vries H (1889) Intracellular pangenesis. Gager CS, transl (1910). Open Court, Chicago

——— (1901–3) Die Mutationstheorie. Veit, Leipzig

——— (1903) Fertilization and hybridization. Paper presented at the 151st annual meeting to the Dutch Society of Science, Haarlem, May 16. Gager CS, transl (included as appendix to De Vries, 1889)

Dronamraju K (1989) The foundations of human genetics. Charles C Thomas, Springfield, IL

East EM (1910) A mendelian interpretation of variation that is apparently continuous. Am Nat 44:65–82

Eyster WH (1924) A genetic analysis of variegation. Genet 9:372–404

Farabee WC (1905) Inheritance of digital malformations in man. Pap Peabody Museum Harvard Univ 3:69–77

Folling A (1934) Uber Ausscheidung von Phenylbreztraubensäure in den Harn als Stoffwechselanomalie in verbindung mit imbezillität. Hoppe Seyler Z Physiol Chem 227: 169–176

Freese E (1959) On the molecular explanation of spontaneous and induced mutations. Brookhaven Symp Biol 12: 63–75

Galton F (1886) Hereditary stature. Nature 33:295–298

Gamow G (1954) Possible relation between deoxyribonucleic acid and protein structure. Nature 173:318

Garrod AE (1908) Inborn errors of metabolism. Lancet 2: 1–7

Goldschmidt R (1938) The theory of the gene. Sci Monogr 46:56–66

Green MM, Green KC (1956) A cytogenetic analysis of the lozenge pseudoalleles in *Drosophila*. Heredity 13:302–315

Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RF, Watkins PCV, et al (1983) A polymorphic DNA marker genetically linked to Huntington's disease. Nature 306:234–238

Ingram VM (1956) A specific chemical difference between the globins of normal human and sickle-cell anemia hemoglobin. Nature 178:792–794

Jackson D, Symons R, Berg P (1972) Biochemical method for inserting new genetic information into DNA of simian virus 40: Circular SV40 DNA molecules containing lambda phage genes and the galactose operon of *E. coli*. Proc Natl Acad Sci USA 69:2904–2909

Jacob F, Monod J (1961) Genetic regulatory mechanisms in the synthesis of proteins. J Mol Biol 3:318–356

Janssens FA (1909) La théorie de la chiasmatypie. Cellule 25:389–411

Johannsen W (1909) Elemente der exakten Erblichkeitslehre. G Fischer, Jena

Kan Y, Dozy A (1978) Antenatal diagnosis of a sickle cell anemia by DNA analysis of amniotic fluid cells. Lancet 2: 910–912

Kevles D (1985) In the name of eugenics. Knopf, New York

Khorana HG (1966) Harvey lectures 1966–1967, ser 62: polynucleotide synthesis and the genetic code. Academic Press, New York, pp 79–105

——— (1979) Total synthesis of a gene. Science 203:614–625

Landsteiner K (1900) Zur Kenntnis der anti-fermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe. Zentralbl Baketeriol Parasitenkd [etc] Jena 28:357–362

Lewis EB (1941) Another case of unequal crossing over in *Drosophila melanogaster*. Proc Natl Acad Sci USA 27: 31–34

——— (1945) The relation of repeats to position effect in *Drosophila melanogaster*. Genetics 30:137–166

Lyon MF (1961) Gene action in the X-chromosome of the mouse (*Mus musculus L.*) Nature 190:372–373

McClintock B (1938) The fusion of broken ends of sister half chromatids following chromosome breakage at meiotic anaphases. Univ Mo Coll Agric Res Bull 290:1–48

——— (1944) The relation of homozygous deficiencies to mutations and allelic series in maize. Genetics 29:478–502

——— (1956) Controlling elements and the gene. Cold

Spring Harbor Symp Quant Biol 21:197–216
McKusick V (1966–90) Mendelial inheritance in man: catalog of autosomal dominant, autosomal recessive, and X-linked phenotypes, 1st–9th eds. Johns Hopkins University Press, Baltimore
McKusick V, Ruddle F (1974) International Workshops on Human Genome Mapping 1973. Cytogenet Cell Genet 1: 216
Maniatis T, Hardison RC, Lacy E, Lauer J, O'Connel C, Quon D, Sim GK, et al (1978) The isolation of structural genes from libraries of eucaryotic DNA. Cell 15:687–701
Maxam AM, Gilbert W (1977) A new method of sequencing DNA. Proc Natl Acad Sci USA 74:560–564
Mendel G (1866) Experiments in plant hybridization. Verhandlungen des Naturforschenden Vereines in Brunn. In: Stern C, Sherwood E (eds) (1966) The origin of genetics: a Mendel source book. WH Freeman, San Francisco, pp 3–47
Miller OL, Beatty BR (1969) Portrait of a gene. J Cell Physiol 74 [Suppl 1]: 225–232
Morgan TH (1910) Sex limited inheritance in Drosophila. Science 32:120–122
——— (1911) Chromosomes and associative inheritance. Science 34:636–638
Morgan TH, Sturtevant AH, Muller JH, Bridges CB (1915) The mechanism of mendelian heredity. Henry Holt, New York
Muller HJ (1918) Genetic variability, twin hybrids, and constant hybrids, in a case of balanced lethal factors. Genetics 3:422–499
——— (1922) Variation due to change in the individual gene. Am Nat 56:32–50
———(1926) The gene as the basis of life. Proc Int Congress Plant Sci 1:897–921
——— (1927) Artificial transmutation of the gene. Science 66:84–87
——— (1928) The problem of genic modification. Proceedings of the Fifth International Congress of Genetics, Berlin, 1927. Z Induktive Abstammungs Vererbungslehre [Suppl 1]: 234–260
——— (1932) Further study on the nature and causes of gene mutations. Proc Sixth Int Congress Genet 1:213–255
——— (1936*a*) Bar duplication. Science 83:528–530
——— (1936*b*) The need of physics in the attack on the fundamental problems of genetics. Sci Mon 44:210–214
Muller HJ, Altenburg E (1919) The rate of change of hereditary factors in *Drosophila*. Proc Soc Exp Biol Med 17:10–14
Muller HJ, Prokofyeva AA (1935) The individual gene in relation to the chromomere and the chromosome. Proc Natl Acad Sci USA 21:16–26
Mullis KB, Faloona FA (1987) Specific synthesis of DNA in vitro via a polymerase catalyzed chain reaction. Methods Enzymol 155:335–350
Nathans D, Smith H (1975) Restriction endonucleases in the analysis and restructuring of DNA molecules. Annu Rev Biochem 44:273–293
Nilsson-Ehle H (1909) Kreuzungsuntersuchungen an Hafer und Weizen. Acta Univ Lundensis (new ser 2) 5:1–122
Nirenberg MW, Matthaei JH (1961) The dependence of cell-free protein synthesis in *E. coli* upon naturally occurring or synthetic polynucleotides. Proc Natl Acad Sci USA 47:1588–1594
Ochoa S (1963) Synthetic polynucleotides and the genetic code. Fed Proc 22:62–74
Offermann CA (1935) The position effect and its bearing on genetics. Izv Akad Nauk SSSR [Biol] 7:452–454
Oliver CP (1940) A reversion to wild type associated with crossing over in *Drosophila melanogaster*. Proc Natl Acad Sci USA 26:452–454
Painter TS (1934) Salivary chromosomes and the attack on the gene. J Hered 25:465–476
Patterson JT (1943) The Drosophilidae of the Southwest. U Tex Publ 4313:8–214
Pauling L, Itano HA, Singer SJ, Wells IC (1949) Sickle cell anemia, a molecular disease. Science 110:543
Pontecorvo G (1942) The problem of dominant lethals. J Genet 43:295–300
——— (1955) Gene structure and action in relation to heterosis. Proc R Sci Biol 144:171–177
Pontecorvo G, Muller HJ (1941) The lethality of dicentric chromosomes in *Drosophila*. Genetics 26:165
Preer J (1948) The killer cytoplasmic factor kappa: its rate of reproduction, the number of particles per cell. Am Nat 82:35–42
Raffel D, Muller HJ (1940) Position effect and gene divisibility considered in connection with three strikingly similar scute mutations. Genetics 25:541–583
Rapoport IA (1948) The effects of ethylene oxide, glycidol, and glycols on gene mutations (in Russian). Dokl Akad Nauk SSSR 60:469–472
Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, Arnheim N (1985) Enzymatic amplification of β-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science 230:1350–1354
Sanger F, Coulson AR (1975) A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. J Mol Biol 94:441–448
Schrödinger E (1945) What is life? Cambridge University Press, Cambridge, and Macmillan, New York
Serebrovsky AS, Ivanova OA, Ferry L (1929) On the influence of genes y, 1, N, on the crossing over close to their loci in the sex chromosome of *Drosophila melanogaster*. J Genet 21:287–314
Sonneborn TM (1949) Beyond the gene. Am Sci 37:33–59
Southern EM (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. J Mol Biol 98:503–517
Spencer H (1864–67) Principles of biology. Privately

printed, London (American ed 1975, D Appleton, New York)

Stadler LJ (1928) Mutations in barley induced by x-rays and radium. Science 68:186–187

Stern C (1929) Uber die additive Wirkung multipler Allele Biol Zentralbl 49:261–290

Stone WS (1949) Survival of chromosome variation in evolution. U Tex Publ 4920:18–21

Sturtevant AH (1913*a*) The himalayan rabbit case, with some considerations of multiple allelomorphs. Am Nat 47:234–238

——— (1913*b*) The linear arrangement of six sex-linked factors in *Drosophila*, as shown by their mode of association. J Exp Zool 14:43–59

——— (1925) The effects of unequal crossing over at the Bar locus in *Drosophila*. Genetics 10:117–147

Sutton WS (1902) Chromosomes in heredity. Biol Bull 4: 231–251

Temin H, Mizutani S (1970) RNA-dependent DNA polymerase in virions of Rous sarcoma virus. Nature 226: 1211–1213

Timofeeff-Ressovsky HA, Timofeeff-Ressovsky NV (1926) Uber das phanotypische Manifesteieren des Genotyps. II. Uber Idiosomatische Variations gruppen bei *Drosophila funebris*. Roux Arch EntwMech Organ 108:146

Tonegawa S (1983) Somatic generation of antibody diversity. Nature 303:585–581

Von Dungern E, Hirszfeld L (1910) Ueber Vererbung gruppenspezifischer Strukturen des Blutes. Z Immunforsch 6: 284–292

Watson JD, Crick FHC (1953*a*) Genetical implications of the structure of deoxyribonucleic acid. Nature 171:964

———(1953*b*) Molecular structure of nucleic acids. Nature 171:737–738

Yanofsky C, Carlton BC, Guest JR, Helinski DR, Henning U (1964) On the colinearity of gene structure and protein structure. Proc Natl Acad Sci USA 51:266–272